[CONTRIBUTION FROM ABBOTT LABORATORIES]

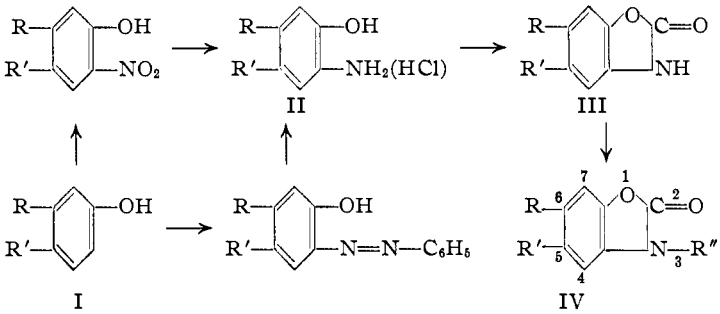
The Analgesic Activity of Some Benzoxazolone Derivatives[1]

BY W. J. CLOSE, BURRIS D. TIFFANY AND M. A. SPIELMAN

Lespagnol and his co-workers[2] were the first to indicate that compounds of the benzoxazolone type may affect the central nervous system. Inasmuch as benzoxazolone is structurally related to 2,4-oxazolidinedione which forms the nucleus of a number of compounds with analgesic and anticonvulsant activity,[3] it seemed desirable to make an extensive search among benzoxazolone derivatives for possible therapeutic application.

The compounds included in this study were N-alkyl, N-acyl, and N-dialkylaminoalkyl derivatives of benzoxazolone and various nuclear substituted derivatives. It was found that a majority of these compounds are capable of inducing mild analgesia in animals.

The preparation of the benzoxazolones required the use of various *o*-aminophenols (II) as intermediates. These were prepared generally through nitration of the corresponding phenol (I), followed by catalytic reduction. In certain cases it was considered more expedient to couple the phenol with benzenediazonium chloride and to reduce the resulting azo derivative chemically. Most of the aminophenols were very sensitive to air oxidation; these were isolated and used in the form of their hydrochlorides.



Usually, the *o*-aminophenol salts were converted to benzoxazolone derivatives (III) by fusion with urea. Though this reaction represents one of the oldest methods of making benzoxazolones,[4] it has received little attention,[5] possibly because it was associated with a poor yield. We have found, however, that yields of 76–90% can be obtained by moderating the temperature and time of reaction. In one case (5,6-dimethylbenzoxazolone) the urea fusion technique failed to give satisfactory yields and the less convenient phosgene method was employed. 6-Chlorobenzoxazolone was prepared in good yield directly from benzoxazolone by chlorination.

The alkylation of the parent benzoxazolones to produce N-substituted derivatives (IV) required considerable experimentation to secure satisfactory results. The use of an alkyl halide in methanolic potassium hydroxide as suggested in the literature[6] usually gave very low yields. By substituting the higher-boiling Cellosolve (glycol monoethyl ether) for methanol, yields of 62–76% were obtained except when secondary halides were used. Somewhat higher yields (generally 80–95% for normal halides) could be obtained by the use of Cellosolve as the solvent and its sodium alkoxide as the basic condensing agent; this method was used for approximately half of the preparations.

Acylation of the benzoxazolones was accomplished easily by treatment of the compound or its sodium salt with acetic anhydride.

Experimental[7]

Preparation of Substituted Phenols

p-**Propylphenol.**—*p*-Propylanisole[8] (289 g.) was demethylated by refluxing three days with a mixture of 450 cc. of 48% hydrobromic acid and 450 cc. of acetic acid into which dry hydrogen bromide was bubbled during the first two hours of reaction. The yield of product was 245 g. (93%); b. p. 79–80° (0.75 mm.).[8]

p-**Amylphenol.**—The following modification of the procedure of Sandulesco and Girard,[9] using a large excess of aluminum chloride, was found to give a three-fold increase in the amount of the desired *p*-hydroxyvalerophenone: Seventy-two grams of phenol dissolved in 144 cc. of nitrobenzene was added to 205 g. of aluminum chloride in 400 cc. of nitrobenzene at 10–12° with stirring. The mixture was treated with 85 g. of valeryl chloride by dropwise addition at 5–10° with stirring. After standing overnight the mixture was poured onto ice and concentrated hydrochloric acid, the layers were separated, and the nitrobenzene layer was extracted with dilute sodium hydroxide. The oil obtained by neutralizing the basic extract was taken up in ether and fractionated to give 108 g. (87%) of the *p*-isomer; b. p. 150–160° (0.6 to 0.8 mm.).

The ketone was reduced by the Clemmensen procedure to give an 85% yield of *p*-amylphenol boiling at 103–107° (1.4 mm.).[10]

(1) Presented in part at the 113th meeting of the American Chemical Society in Chicago, April 20, 1948.

(2) Lespagnol, Durbet and Mongy, *Compt. rend. soc. biol.*, **135**, 1255 (1941); Lespagnol and Lefebvre, *Bull. soc. chim.*, **12**, 386 (1945).

(3) Spielman, THIS JOURNAL, **66**, 1244 (1944); Spielman and Everett, *ibid.*, **70**, 1021 (1948).

(4) Sandmeyer, *Ber.*, **19**, 2656 (1886).

(5) The fusion of the free aminophenol with urea was used to prepare benzoxazolone in 35% yield by Bywater, Coleman, Kamm and Merritt, THIS JOURNAL, **67**, 905 (1945). Since the inauguration of the present work, Williams [*Biochem. J.*, **41**, 4 (1947)] has reported a 76% yield from the fusion of the free base and urea by a procedure similar to ours.

(6) Ransom, *Am. Chem. J.*, **23**, 33 (1900).

(7) Microanalyses by E. F. Shelberg and staff. High pressure hydrogenations by M. Freifelder.

(8) Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 520 (1945).

(9) Sandulesco and Girard, *Bull. soc. chim.*, [4] **47**, 1309 (1930).

(10) Ref. 9, p. 1310.

Preparation of Substituted ortho-Aminophenols

2-Amino-4-methylphenol.—2-Nitro-4-methylphenol[11] was dissolved in absolute alcohol and reduced with Raney nickel at 75° under a hydrogen pressure of 1000 pounds. After removal of the catalyst by filtration and evaporation of the solvent, the basic residue was treated with a slight excess of alcoholic hydrogen chloride. Anhydrous ether was then added to precipitate the hydrochloride in 90% yield; m. p. 222–224° (dec.).[12]

2-Amino-4-propylphenol.—A modification of the Baranger[11] procedure gave 83% of 2-nitro-4-propylphenol; b. p. 92–96° (0.85 mm.); $n^{25}D$ 1.5574.

Anal.[13] Calcd. for $C_9H_{11}NO_3$: N, 7.7. Found: N, 7.7.

Catalytic reduction as described above gave 98% of the aminopropylphenol hydrochloride; m. p. 245–252° (dec.).

Anal. Calcd. for $C_9H_{13}NO\cdot HCl$: N, 7.5. Found: N, 7.6.

2-Amino-4-amylphenol.—A solution of 51 cc. of concentrated nitric acid in 100 cc. acetic acid was cooled to −10° and 65 g. of *p*-amylphenol dissolved in 65 cc. of acetic acid was added with stirring over a period of two hours. The temperature was maintained below −5° during the addition. The reaction mixture was immediately poured into a mixture of ice and 160 g. of 10% sodium hydroxide, and extracted with benzene. The benzene extract was steam distilled and the oil so obtained was distilled to give 61.8 g. (75%) of 2-nitro-4-amylphenol; b. p. 100–105° (0.5 mm.); $n^{25}D$ 1.5253.

Anal. Calcd. for $C_{11}H_{15}NO_3$: N, 6.7. Found: N, 6.9.

The nitro derivative was reduced as described above to give 84% of the hydrochloride which melted at 194° after recrystallization from alcohol.

Anal. Calcd. for $C_{11}H_{17}NO\cdot HCl$: N, 6.5. Found: 6.5.

The free base, obtained by neutralization of the hydrochloride and recrystallization from petroleum ether, melted at 128°.

Anal. Calcd. for $C_{11}H_{17}NO$: N, 7.8. Found: N, 8.0.

2-Amino-4,5-dimethylphenol.—2-Benzeneazo-4,5-dimethylphenol[14] was reduced by sodium hydrosulfite in basic solution to give 77% of aminophenol melting at 171–175°.[15]

2-Amino-4-methoxyphenol.—One mole of diazotized aniline was added over a period of 1.5 hours to a solution of 124 g. of hydroquinone monomethyl ether dissolved in 1200 cc. of water containing 120 g. of sodium hydroxide. The temperature was maintained at −5 to 0° during the addition. The mixture was filtered, and the filtrate acidified to yield 202 g. (89%) of 2-benzeneazo-4-methoxyphenol; m. p. 69–72°. A pure sample was prepared as dark red needles from alcohol; m. p. 72.5–73.5°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: N, 12.3. Found: N, 12.5.

The azo derivative was reduced by dissolving 100 g. in 1 l. of water containing 100 g. of sodium hydroxide. The solution was warmed on the steam-bath and sodium hydrosulfite was added in portions with stirring until the color was discharged. The aniline formed was extracted with ether; neutralization of the basic solution precipitated the aminophenol which was filtered rapidly, pressed as dry as possible on the filter plate, and immediately triturated with ethereal hydrogen chloride to give 57.5 g.; m. p. 205–212° (dec.). An additional 7.8 g., m. p. 197–205°, isolated from the aqueous filtrate by ether extraction and precipitation with ethereal hydrogen chloride brought the yield to 85%. The hydrochloride could be recrystallized only with considerable loss. An analytically pure sample was obtained from alcohol, using Norit. The m. p. was 210–213° (dec., pyrex tube evacuated to 0.5 mm.). Roberts and co-workers[16] reported a m. p. of 171° for the product obtained by the reduction of 2-nitro-4-methoxyphenol.

Anal. Calcd. for $C_7H_9NO_2\cdot HCl$: N, 8.0. Found: N, 7.8.

Preparation of Parent Benzoxazolones

The urea-fusion method (Method A), which was used for the preparation of most of the parent compounds, is illustrated by the preparation of 5-propylbenzoxazolone. Benzoxazolones not prepared by fusion with urea were synthesized as described below. The properties of all the compounds are given in the accompanying table.

Method A. 5-Propylbenzoxazolone.—2-Amino-4-propylphenol (470 g.) was intimately mixed with 300 g. of urea and heated in an oil-bath at 180° for two hours. The reaction mixture was cooled somewhat and acidulated water was added. The oil which separated was taken up in ether, concentrated and distilled. The product (348 g., 79%) boiled at 180–182° (0.8 mm.) and solidified in the receiver.

5,6-Dimethylbenzoxazolone.—A suspension of 34.2 g. of 2-amino-4,5-dimethylphenol and 59 g. of anhydrous potassium acetate in 600 cc. of ethyl acetate was treated dropwise with 30 g. of phosgene in 400 cc. of ethyl acetate with vigorous stirring. After refluxing briefly, water was added and the ethyl acetate layer separated. After washing with water and 5% hydrochloric acid, the solvent was removed. The residue of crude product was best purified by dissolving in boiling 10% NaOH and cooling in ice. The sodium salt which precipitated was suspended in water and acidified. By reworking the basic filtrate, a total of 27.6 g. (68%) of material melting at 173–177° was obtained.

6-Chlorobenzoxazolone.—Benzoxazolone (50 g.) was dissolved in 500 cc. of acetic acid, cooled in ice, and treated with 32 cc. of sulfuryl chloride with stirring. After standing overnight at room temperature, the solution was warmed on the steam-bath for one hour, cooled, and poured into water. A total of 51.3 g. (81%), m. p. 189–194°, was obtained.

The position of the chloro group was demonstrated by cleavage of the oxazolone ring with sodium hydroxide to give a chloroaminophenol. Purification of the product gave prismatic needles, m. p. 152–154° (dec.). The melting point was undepressed when mixed with a sample of 2-amino-5-chlorophenol, m. p. 152–154°, prepared according to Theilacker.[17]

Alkylation of Benzoxazolones

The following examples illustrate the two general methods used to convert the parent benzoxazolones into N-substituted derivatives. The accompanying table lists the compounds prepared by these methods together with their properties.

Method B. 3-*iso*-Amyl-5-propylbenzoxazolone.—5-Propylbenzoxazolone (6.2 g.) was dissolved in 60 cc. of 0.84 *N* KOH in Cellosolve. *iso*-Amyl iodide[18] (9.3 cc.) was added and the mixture was refluxed for six hours. The liquid was decanted from the precipitate of potassium iodide and concentrated under reduced pressure. The residue was taken up in benzene and water; the benzene layer was separated and washed with 5% sodium hydroxide and water. After removal of the benzene, the product was distilled to give 5.7 g. (66%); b. p. 148–150° (0.8 mm.).

Method C. 3-Amyl-5-methoxybenzoxazolone.—A small flask was fitted with a reflux condenser, stirrer, dropping funnel, and short gas inlet tube. A slow stream of nitrogen was passed through the inlet tube during the course of reaction. Thirty cc. of Cellosolve (purified by distillation from sodium dissolved in Cellosolve) was introduced into the flask, and 1.6 g. of sodium was dissolved

(11) Baranger, *Bull. soc. chim.*, [4] **49**, 1217 (1931).

(12) Wagner, *Ber.*, **7**, 1270 (1874).

(13) No analyses reported in original preparation.

(14) (a) Diepolder, *Ber.*, **42**, 2918 (1909); (b) **44**, 2498 (1911).

(15) Ref. 14a, p. 2920; ref. 14b.

(16) Roberts, de Worms and Clark, *J. Chem. Soc.*, 198 (1935).

(17) Theilacker, *Ber.*, **71B**, 2070 (1938).

(18) There appeared to be no advantage in using iodides in place of bromides. Bromides were used exclusively in Method C.

TABLE I

PROPERTIES OF BENZOXAZOLONE DERIVATIVES

Substituents Nuclear	Nitrogen	B. p.,[a] °C.	Mm.	$n^{25}D$[a]	M. p.,[a] °C.	Formula	Nitrogen, % Calcd.	Found	Prep. meth.	Yield, %	Act.[b]
None	H[c]	.....		....	139–140	.....	..	..	A	88	....
None	CH_3[d]	.....		....	83–84	.....	..	..	..[d]	..	±
None	n-C_4H_9	129–130	1.3	1.5316	.....	$C_{11}H_{13}NO_2$	7.3	7.3	B	62	0
None	i-C_4H_9	.....		....	63.5–65[e]	$C_{11}H_{13}NO_2$	7.3	7.3	B	76	0
None	n-C_5H_{11}	140–142	1.0	1.5268	.....	$C_{12}H_{15}NO_2$	6.8	6.9	..[f]	40	0
None	i-C_5H_{11}	112–113	0.4	1.5248[g]	40–40.5[e]	$C_{12}H_{15}NO_2$	6.8	6.8	C	90	+++[h]
None	s-C_5H_{11}	132–134	1.3	1.5280	.....	$C_{12}H_{15}NO_2$	6.8	7.0	B	40	++
None	Acetyl[i]	.....		....	92–94	.....	..	..	..[i]	66	0
None	Allyl[j]	112–114	0.5	1.5536	.....	$C_{10}H_9NO_2$	8.0	8.1	C	66	0
None	....[k]	.....		....	171–173[k]	$C_{13}H_{19}ClN_2O_2$	10.3	10.3	C	66	++
5-CH_3	H[l]	.....		....	128–129	.....	..	..	A	79	0
5-CH_3	n-C_4H_9	138–140	1.2	1.5300	.....	$C_{12}H_{15}NO_2$	6.8	7.0	B	67	++
5-CH_3	i-C_4H_9	.....		....	61–62[e]	$C_{12}H_{15}NO_2$	6.8	7.1	B	70	±
5-CH_3	n-C_5H_{11}	136–138	0.8	1.5239	.....	$C_{13}H_{17}NO_2$	6.4	6.5	B	65	+
5-CH_3	i-C_5H_{11}	142–143	1.3	1.5230	.....	$C_{13}H_{17}NO_2$	6.4	6.3	B	65	±
5-CH_3	s-C_5H_{11}	130–133	1.2	1.5251	.....	$C_{13}H_{17}NO_2$	6.4	6.6	B	54	....
5-n-C_3H_7	H	.....		....	66.5–68[m]	$C_{10}H_{11}NO_2$	7.9	7.7	A	79	0
5-n-C_3H_7	n-C_4H_9	164–167	1.0	1.5196	.....	$C_{14}H_{19}NO_2$	6.0	6.1	C	95	+++[h]
5-n-C_3H_7	i-C_4H_9	141–144	1.2	1.1597	.....	$C_{14}H_{19}NO_2$	6.0	6.1	B	65	++
5-n-C_3H_7	n-C_5H_{11}	162–164	1.4	1.5157	.....	$C_{15}H_{21}NO_2$	5.7	5.7	B	66	++
5-n-C_3H_7	i-C_5H_{11}	148–150	0.8	1.5167	.....	$C_{15}H_{21}NO_2$	5.7	5.9	B	66	0
5-n-C_3H_7	s-C_5H_{11}	148–151	1.1	1.5197	.....	$C_{15}H_{21}NO_2$	5.7	5.9	B	38	+
5-n-C_5H_{11}	H	.....		....	62–64[n]	$C_{12}H_{15}NO_2$	6.8	6.8	A	90	....
5-n-C_5H_{11}	CH_3	.....		....	55–56.5[n]	$C_{13}H_{17}NO_2$	6.4	6.5	..[o]	96	....
5-n-C_5H_{11}	n-C_3H_7	167–170	2.0	1.5180	.....	$C_{15}H_{21}NO_2$	5.7	5.8	C	94	0
5-n-C_5H_{11}	i-C_4H_9	146–148	0.6	1.5144	.....	$C_{16}H_{23}NO_2$	5.4	5.3	C	90	+
5-n-C_5H_{11}	n-C_5H_{11}	178–180	1.4	1.5115	.....	$C_{17}H_{25}NO_2$	5.1	5.0	C	93	0
5,6-diCH_3	H	.....		....	177–178[p]	$C_9H_9NO_2$	8.6	8.4	..[q]	68	++
5,6-diCH_3	C_2H_5	.....		....	86–87[r]	$C_{11}H_{13}NO_2$	7.3	7.3	..[s]	73	++
5,6-diCH_3	n-C_4H_9	.....		....	68–69[t]	$C_{13}H_{17}NO_2$	6.4	6.3	C	80	0
5,6-diCH_3	i-C_5H_{11}	.....		....	50–51[u]	$C_{14}H_{19}NO_2$	6.0	6.2	C	86	++
5-CH_3O	H	.....		....	170–172[v]	$C_8H_7NO_3$	8.5	8.2	A	76	++
5-CH_3O	i-C_4H_9	.....		....	57–58[w]	$C_{12}H_{15}NO_3$	6.3	6.2	C	87	++
5-CH_3O	n-C_5H_{11}	168–172	1.4	1.5299	.....	$C_{13}H_{17}NO_3$	6.0	5.8	C	92	++
5-CH_3O	Acetyl	.....		....	102–103[p]	$C_{10}H_9NO_4$	6.8	6.7	..[q]	95	++
6-Cl	H	.....		....	194–195[x]	$C_7H_4ClNO_2$	8.3	8.3	..[q]	81	....
6-Cl	CH_3	.....		....	104–105[x]	$C_8H_6ClNO_2$	7.6	7.6	..[o]	85	0
6-Cl	i-C_3H_7	.....		....	91–92[r]	$C_{10}H_{10}ClNO_2$	6.6	6.4	C	40	+
6-Cl	i-C_5H_{11}	157–163	1.0	1.5308[g]	46–47[y]	$C_{12}H_{14}ClNO_2$	5.8	5.9	C	62	+++

[a] Data for analytically pure sample. [b] The symbols express the increase in pain threshold according to the following scale: 0 = none; ± = doubtful; + < 10%; ++ = 10–20%; +++ = 20–30%. [c] Bywater, Coleman, Kamm and Merritt, THIS JOURNAL, **67**, 905 (1945). [d] Ransom, *Am. Chem. J.*, **23**, 33 (1900). [e] Prisms from pentane. [f] Reaction carried out using potassium hydroxide in ethylene glycol. [g] Data on supercooled liquid. [h] Tested in human volunteers with lower results. [i] Kalckhoff, *Ber.*, 16, 1828 (1883). [j] Reported by Lespagnol, Durbet and Mongy, *Compt. rend. soc. biol.*, **135**, 1255 (1941), with no details given. [k] Diethylaminoethyl hydrochloride; two crystallographic forms; lower form obtained as prisms from acetone–alcohol, m. p. 140–147° with resolidification and conversion to higher form. [l] Upson, *Am. Chem. J.*, **32**, 17 (1904). [m] Needles from pentane. [n] Needles from petroleum ether. [o] Reaction carried out using sodium methoxide and dimethyl sulfate in methanol. [p] Needles from alcohol. [q] Specific preparation described in text. [r] Needles from alcohol-petroleum ether. [s] Prepared with sodium ethoxide and diethyl sulfate in ethanol. [t] Two crystallographic forms; lower form obtained as prisms from petroleum ether, m. p. 61–63° with resolidification and conversion to higher form. [u] Needles from dilute alcohol. [v] Prisms from alcohol. [w] Prisms from alcohol–petroleum ether. [x] Leaflets from alcohol. [y] Leaflets from petroleum ether.

in the solvent. 5-Methoxybenzoxazolone (9.9 g.) was stirred into the solution, followed by 9.6 cc. of *n*-amyl bromide.[18] The solution was refluxed for one hour, then retreated with 0.69 g. of sodium dissolved in 10 cc. of Cellosolve (solution prepared under nitrogen) and 4.8 cc. of bromide. Refluxing was continued for one hour.

The reaction mixture was acidified with acetic acid and concentrated under reduced pressure. The residue was treated with ether and water. The separated ether layer was washed with water, 5% sodium hydroxide, 5% hydrochloric acid, and water. The ether was removed and the residue was distilled to give 13.0 g. (92%); b. p. 166–174° (1.0 mm.).

Acylation of Parent Benzoxazolones

N-Acetyl derivatives of two benzoxazolones were prepared (see table). The following procedure gave the best results.

3-Acetyl-5-methoxybenzoxazolone.—A solution of 1.6 g. of sodium in 50 cc. of methanol was prepared and 9.9 g. of

5-methoxybenzoxazolone was added. The solvent was removed under reduced pressure and the dry solid residue was treated with 25 cc. of acetic anhydride. The mixture was swirled thoroughly and allowed to stand for ten minutes, after which it was poured into water. The product was filtered to give 11.8 g. (95%); m. p. 100–103°.

Pharmacologic Evaluation

The compounds were tested for analgesic activity in dogs by a modification of the method of Andrews and Workman.[19] These determinations were carried out by Dr. R. K. Richards and Mr. K. E. Kueter of our laboratories to whom we express our thanks. Doses of 100–200 mg./kg. were used, at which level toxic symptoms rarely appeared. Several of the derivatives raised the pain threshold 10–20%; a few 20–30%. The best compounds, therefore, have an activity comparable to that of aspirin, which gives a 15–20% increase in 100 mg./kg. doses. They are much weaker analgesics than Demerol, which is capable of raising the pain threshold 30–40% in 15 mg./kg. quantities. Pharmacologic data for all of the benzoxazolones tested are included in the table.

(19) Andrews and Workman, *J. Pharmacol.*, **73**, 99 (1941).

Summary

1. The synthesis of approximately forty N-alkyl, N-acyl, and N-dialkylaminoalkyl derivatives of benzoxazolone and nuclear substituted benzoxazolones is described.

2. About two-thirds of the derivatives induced mild analgesia in dogs.

RECEIVED AUGUST 7, 1948

[CONTRIBUTION FROM THE DIVISION OF ORGANIC CHEMISTRY, SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Streptomycin. XII. Streptamine Isomers from *meso*-Inositol

BY A. E. O. MENZEL,[1] M. MOORE AND O. WINTERSTEINER

In 1915 Griffin and Nelson,[2] in a study of the action of acetyl bromide on *meso*-inositol, obtained besides other products two isomeric dibromotetraacetoxycyclohexanes, melting at 225 and 130°, respectively, which Müller[3] had previously prepared from *meso*-inositol in a slightly different manner. In the absence of information on the position of the bromine atoms the higher-melting isomer was arbitrarily termed α-, and the lower melting isomer, β-. Soon after the structure of streptamine had been established,[4,5] we began an investigation of the aminolysis of these compounds and of the corresponding dibromotetrols (of which only the β-isomer had been previously described[2]), in the hope to arrive, if not at streptamine itself, at some isomers of it. While Griffin and Nelson were unable to effect amination of the β-dibromotetraacetoxycyclohexane by treatment with liquid ammonia at room temperature, we found that both the α- and the β-dibromotetrol reacted with aqueous ammonia at 100° with the formation of diamines. The crude products were isolated as picrates, which in both cases could be separated into a methanol-soluble fraction (I) and a much smaller methanol-insoluble fraction (II). The four picrate fractions were purified by recrystallization and converted to dihydrochlorides. The two pairs of diamines thus obtained are designated here for convenient reference as α- and β-diamines I, and α- and β-diamines II, the Greek letters signifying derivation from the corresponding dibromotetrol isomers, and the Roman numerals derivation from the methanol-soluble and methanol-insoluble picrate fraction, respectively. They were converted into suitable acyl derivatives for comparison with each other and with streptamine.

As could be anticipated from the properties of the salts and acyl derivatives of streptamine, the crystal shape and melting point data were of limited value as criteria for establishing identity or non-identity because the new compounds were generally microcrystalline and melted or decomposed over a considerable range. This was for instance the case with the dipicrates, sulfates, N,N′-diacetates and hexaacetates of α-diamine I and β-diamine I, respectively. Notwithstanding these limitations the picrates, sulfates and hexaacetates showed such close correspondence of their properties that identity of the parent diamines was at first suspected. Subsequently, however, certain differences in melting point behavior were observed with the N,N′-diacetates and the hexabenzoates. Particularly with the latter pair these discrepancies could not be dismissed as being due to accidental causes, because both compounds, in contradistinction to the acetyl derivatives, exhibited fairly well-defined melting points. Thus, while the β-hexabenzoate melted at 262–263°, it was not possible to raise the melting point of the α-hexabenzoate beyond 252–255°, and a small but distinct depression (251–253°) was observed in mixture. Furthermore, the X-ray diffraction patterns[6] of the two compounds were quite dissimilar, but the significance of this finding is not quite clear in view of the fact that the pattern given by the α-hexabenzoate raised some doubt as to its completely crystalline character (*cf.* Experimental). Nevertheless, we believe that the weight of the evidence is against identity, and that α-di-

(1) Present address: Roosevelt Hospital, W. 59th St., New York 19, N. Y.

(2) E. G. Griffin and J. M. Nelson, THIS JOURNAL, **37**, 1552 (1915).

(3) H. Müller, *J. Chem. Soc.*, **91**, 1788 (1907).

(4) R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo and K. Folkers, THIS JOURNAL, **68**, 776 (1946).

(5) H. E. Carter, R. K. Clark, Jr., S. R. Dickman, Y. H. Loo, P. S. Skell and W. A. Strong, *Science*, **103**, 540 (1946).

(6) We are greatly indebted to Prof. G. L. Clark, of the Department of Chemistry, University of Illinois, for these measurements.